Remarks

1. Elections/Restrictions

Applicants hereby cancel claims 19 and 40 – 50 in view of the maintenance of the restriction requirement imposed previously. For the reasons noted in our 7/22/02 response, we disagree with the rationale, necessity, benefit and appropriateness of this exercise of the PTO's discretionary authority, but have no choice at this point but to cancel these claims. Applicants do request that, upon a finding of patentable subject matter in the remaining claims, this issue be revisited and examination of some or all of the claims now canceled be reconsidered.

2. Drawings

The Drawings have been replaced as required by the Examiner.

3. Claim Objections

Claim 12 was already believed to refer to other claims in the alternative. The Examiner disagreed. Accordingly, claim 12 has been amended to accommodate the Examiner. It now clearly refers to claims 5 – 11 in the alternative. The amendment is formalistic in nature and is not intended to change the meaning or scope of the claim or introduce any new matter. The objection to all remaining claims based on the wording of claim 12 is now believed to be moot.

Claims 12 and 35 have also been amended to remove unintentional residual brackets from the previous amendments. Applicants thank the Examiner for pointing out this clerical error.

Claim 29 has been amended to highlight, at a now earlier point in its text, the fact that the claimed cell is an isolated cell. The amendment is formalistic in nature and is not intended to change the meaning or scope of the claim or introduce any new matter. We assume the Examiner agrees that an isolated human cell is distinct from a transgenic human being since transgenic human beings are not made up of isolated human cells. Those cells which taken together make up a human being are by definition, not isolated in that context.

4. Claim Rejections -- 35 USC § 112, 1st paragraph

(a) *Rejection of claims to engineered host cells and methods for making them, based on alleged non-enablement of transgenic animals.*

Claims 26, 28, 30, 32, 34 and 38 relate to genetically engineered host cells containing a recombinant nucleic acid of the invention, that is, the cells per se, cells encapsulated in a biocompatible material and/or present in a non-human organism, and methods for making such cells. Those claims stand rejected for alleged lack of enablement to the extent the claims read on transgenic animals.

First, we note that there is a long history of issued US patents, issued long before and long after the filing of the subject application, which contain claims to genetically engineered host cells (etc) yet whose specifications provide no additional disclosure of transgenic animal technology relative to applicants' specification—that is, if they even mention transgenic technologies. If all of those claims of all of those issued patents are still considered patentable, then so should applicants' claims in question. Applicants respectfully request that their application be examined using the same high level of scrutiny that was applied in all those other cases, and that no new hurdles be imposed specially for us. On this basis, we request reconsideration and withdrawal of this ground for rejection.

Second, to pick one presumed embodiment out of many embodiments of a claimed invention, label it non-enabled and use that as a ground for rejecting the generic claims seems heavy handed and arbitrary. It is well settled that the validity of a claim is not undone by the possible inclusion of an inoperative embodiment. How could it be undone then by a failure to enable an allegedly outlying embodiment, the operability of which is irrelevant? On this basis too, we request reconsideration and withdrawal of this ground for rejection.

Third, in this case, we dispute the existence of any deficiency in the specification. Here the rejection is based, not on an alleged inadequacy in description of the recombinant nucleic acids or the use of additional technology not already well known in the art. The Examiner

agrees that many patents on transgenic animals have been issued. The Examiner doesn't dispute that technology for creating transgenic animals was already known or that transgenic animals can be made. The Examiner lists a number of experimental variables, but variable which are known in the art and are routinely manipulated by the transgenic practitioner. Many are design choices available to the practitioner who chooses among them in the ordinary practice of his or her craft, depending on the goal of the exercise and routine experimental and individual factors. Those who want transgenic animals are even able to send their recombinant nucleic acid to any number of companies who for a fee will gladly create the desired transgenic animals using one of several available technologies, often at the choice of the purchaser. Simply Google the words "transgenic animal production" to get a taste of what is available.

The issue is not potential experiment to-experiment variability as urged by the Examiner. That issue has not stopped the widespread development and deployment of transgenic technology. The overall results are clear: transgenic animal production is do-able and is in fact done despite the variables noted by the Examiner.

As we pointed out last time, the US Government not only patented some of this technology, but also created a national database of targeted mouse mutations and transgenic mice in the early 1990's. But again, it appears that the Examiner hasn't doubted the availability in the art of all of the necessary technology.

In view of the foregoing, applicants' specification already provides all that the law requires and then some. We respectfully point the Examiner again to pages 2 –5 of applicants 7/16/2002 response in this case for additional specifics. On this basis as well, we request reconsideration and withdrawal of this ground for rejection.

(b) *Rejection of claims to engineered host cells and methods for making them, based on allegations of (i) lack of guidance correlating expression of transgene with any particular effect in vivo, (ii) failure to state uses for expressing the transgene other than to provide a therapeutic effect, and (iii) unpredictability of obtaining a therapeutic effect following transgene expression in gene therapy*

Claims 26, 30, 34, 36 and 38 relate to genetically engineered host cells containing a recombinant nucleic acid of the invention, that is, the cells per se, cells encapsulated in a biocompatible material and/or present in a non-human organism, and methods for making such cells. Those claims stand rejected for alleged lack of enablement in that applicants allegedly fail to provide required guidance correlating expression of a CAB recombinant nucleic acid in a cell in vivo with any particular effect, i.e., a therapeutic effect, since that is the only use seen for such gene expression in vivo. Moreover, the Examiner asserts again that obtaining therapeutic effects from gene expression in gene therapy is unpredictable.

Here are several serious problems with that basis for rejection, each of which justifies withdrawal of the rejection:

(i) First, again, we note that there is a long history of issued US patents, issued long before and long after the filing of the subject application, which contain claims to genetically engineered host cells (etc) yet whose specifications provide no additional disclosure, relative to applicants' specification, of the introduction of genes in vivo—that is, <u>if they even mention in vivo gene delivery</u>. Again, how can we explain that discrepancy? As noted above, applicants respectfully request that their application be examined using the same high level of scrutiny that was applied in all those other cases, but that no arbitrary lines be drawn specially for us. On this basis, we request reconsideration and withdrawal of this ground for rejection.

(ii) Second, claim 30 is directed to encapsulated cells. Was the inclusion of that claim in this rejection intentional? Since the rejection is based on the in vivo gene therapy rationale, the rationale for including claim 30 is unclear.

(iii) Third, in contrast to the position set forth in the Office Action that the evidence of record has not provided other uses for expressing a CAB protein in vivo other than to provide a therapeutic effect, we direct the Examiner's attention, e.g., to page 68 of the specification for a discussion of uses of the invention to evaluate the function of various genes and gene products in animal models. And lest such research uses be improperly discounted, applicants direct the Examiner's attention to the June 2003 CAFC case of Integra Life Sciences v Merck KGaA (No. 02-1052, -1065). We also note that applicants previously identified this use on page 2 of their 7/16/2002 response in this case.

(iv) Finally, even if, arguendo, the effect of certain gene therapy experiments in humans is deemed unpredictable, and despite the various opinions selected from their various contexts in the pending and prior Office Actions—the transfer of genes in vivo using a variety of viral and non-viral means and in a wide variety of species including insects, worms, rodents and other mammals, including non-human primates and, yes, humans as well, has been well documented. As we noted in our 7/16/2002 paper in this case:

> The scientific literature provides many examples of stable, useful gene expression from transgenes in numerous mammals including mice, goats, pigs, cows, and sheep. For instance, Harvard's US Patent 5,087,571 summarizes numerous examples in the following passage:
>
> > "Wagner et al. (1981) P.N.A.S. U.S.A. 78, 5016; and Stewart et al. (1982) Science 217, 1046 describe transgenic mice containing human globin genes. Constantini et al. (1981) Nature 294, 92; and Lacy et al. (1983) Cell 34, 343 describe transgenic mice containing rabbit globin genes. McKnight et al. (1983) Cell 34, 335 describes transgenic mice containing the chicken transferrin gene. Brinster et al. (1983) Nature 306, 332 describes transgenic mice containing a functionally rearranged immunoglobulin gene. Palmiter et al. (1982) Nature 300, 611 describes transgenic mice containing the rat growth hormone gene fused to a heavy metal-inducible metalothionein promoter sequence. Palmiter et al. (1982) Cell 29, 701 describes transgenic mice containing a thymidine kinase gene fused to a metalothionein promoter sequence. Palmiter et al. (1983) Science 222, 809 describes transgenic mice containing the human growth hormone gene fused to a metalothionein promoter sequence."

Gene expression in a wide variety of such cases has been studied and reported. See also, e.g., the 7-page partial survey (attached to applicants 7/16/2002 response) of the patent and scientific literature dealing with the delivery of genes in vivo using, as an example, AAV gene delivery systems as alluded to in applicants' specification.

Whether a therapeutic effect has been seen (in cases in which it was relevant) is a question for the FDA and is certainly *irrelevant* to this prosecution. As a matter of law applicants' specification has provided more than ample, enabling support for the pending claims. Applicants told the practitioner what to make, why to make it, how to make it and how to deliver it, among other important items of practical information. In different cases different results will be obtained, and indeed, will be sought. Yes, mileage may vary, but as is expected in the art and not because of a deficiency of disclosure by applicants.

As noted in our previous response, the disclosure fills nearly 100 pages of text, describing the following, among other aspects:

- the operative design principles for designing and using CAB fusion proteins (see Summary of the invention and discussion on pages 16 – 21),
- specific details on nucleic acid sequences to start with (see e.g. the chart on p. 26),
- heterologous domains which may be included in the fusion protein design (see e.g. pp. 28 – 29)
- mutations that may be incorporated (see e.g. FKBP discussion on pages 21 – 24, cyclophilin discussion on p. 24, CAB discussion on pages 24 – 28)
- various ligands which may be used with the CAB fusion proteins (see e.g. pp. 33 – 34),
- additional components and design features which may be included (see e.g. pp. 34 – 35),
- tissue-specific or cell-type specific expression (see e.g. pp. 35 – 38, including chart of illustrative genes whose promoters/enhancers permit tissue-specific expression, with references, in many cases to transgenic animal experiments)
- target genes for heterologous expression (see e.g. pp 39 – 42)
- principles and practical guidance on design and assembly of DNA constructs (see e.g. pp 42 – 44)
- principles and practical guidance on the delivery of nucleic acids to cells ex vivo and in vivo (see disclosure beginning on p. 44 and continuing through viral vector systems on pp. 45 – 58, administration of viral vectors to recipients (p. 58 – 62)
- ligand binding properties and their measurement and comparison (see e.g. pp. 62 – 65)
- illustrative applications of the invention (see e.g. pp 65 - 68—including gene therapy, production of recombinant proteins and viruses, production of protein or RNA for biochemical purification, regulated expression of protein or RNA of interest for evaluation of function. etc.)
- practical guidance on formulation and administration of various materialsof the invention (see e.g. pp 68 – 72)
- 25 pages of specific examples
- 10 sheets of figures
- copious citations throughout the document to helpful references in the scientific and patent literature

In view of the foregoing comments and in the face of applicants' specification, we respectfully request that the Examiner reconsider and withdraw all enablement rejections lodged against the pending claims.

5. Claim Rejections -- 35 USC § 112, 2nd paragraph

According to the Examiner, the "lack of a uniform numbering system of amino acids known in the art" and the absence of sequences for calineurin A or B proteins or nucleic acids renders claims indefinite. Furthermore, the inclusion of GenBank accession numbers was said to be improper and impermissible. For those reasons, the portions of Calcineurin A and B referred to in the claims and specification are undefined, and the skilled artisan would not know what sequences to use.

First, on the inclusion of GenBank accession numbers: those numbers were present in the application as filed (see chart, page 26), and no valid reason has been set forth as to why their inclusion is improper. We are aware of no prohibition in the MPEP on this matter.

Second, peptide and nucleotide sequences for numerous Calcineurin A and B species are and were known in the art. The table on page 26 of the specification identifies references in the scientific literature to Human, Rat, Bovine and Mouse Calcineurin A and Calcineurin B sequences and provides GenBank accession numbers for the practitioner's convenience.

The cited references provide background information and sequence information—numbered. For instance, Guerini and Klee, PNAS 86, (1989) cited in the table on page 26 of the specification provides an overlay of human and bovine sequence (see page 9186) and makes frequent reference to numbered locations in the sequences. See e.g. the reference to residues 1-341, 42-338 and 256 – 262 on page 9185, with reference to the depicted sequence.

Further eliminating the possibility of any ambiguity, the specification provides working examples and reference points to numbered portions of Cal A and B. See e.g. page 25, lines 33 – 36 and the first full paragraph on page 26 of the specification.

Calcineurin A and B species are known and defined in the art. They are referenced and relevant portions are confirmed in the specification using the terminology and methodology accepted and relied upon in the art. Thus, the references in the claims to portions of Calcineurin A and Calcineurin B would be viewed by the routine practioner in this art as reasonably definite, and that is what the law requires. Accordingly, reconsideration and withdrawal of this ground for rejection is respectfully requested.

6. Claim Rejections -- 35 USC § 102

Claims 1 - 4, 11, 20 - 21, 26, 28, 34, and 36 remain rejected under 35 USC § 102(b) as being unpatentable over Guerini et al. (PNAS) or Guerini et al. (DNA) which relate respectively to the cloning of under Calcineurin A and B. Claim 1 contains the functional limitation that the encoded CAB domain forms a tripartite complex with an FKBP domain and appropriate ligand. That limitation is a straightforward functional limitation which helps define the claimed subject matter. It is not a mere statement of intended use. Neither reference discloses that limitation, and as a matter of law, neither reference can therefore anticipate claim 1 or the other claims which directly or indirectly contain that limitation. Accordingly, this ground for rejection should be reconsidered and withdrawn.

7. Claim Rejections -- 35 USC § 103

Claims 1, 5 - 11, 20, 23, 26, 28, 34, and 36 remain rejected under 35 USC § 103(a) as being unpatentable under Guerini et al. (PNAS) or Guerini et al. (DNA) taken with Chaudhuri et al. and Crabtree (US 6,164,787).

Yes, the Guerini papers disclose separately the two Calcineurins, and Chaudhuri et al and Crabtree disclose fusion proteins and their use In two- and three-hybrid systems. But none of these references discloses the possibility or desirability of designing fusion proteins using portions of Calcineurin A and Calcineurin B such that the Calcineurin A-B fusion forms a tripartite complex with an FKBP domain and ligand therefore.

Again, forming the recited tripartite complex is a limitation of the claims which is neither disclosed nor suggested by the cited art, taken separately or in combination. It is only in the rearview mirror provided by applicants' specification that the combination asserted in the Office Action takes shape.

As we pointed out last time, the critical issue for the §103 analysis is whether any of the references themselves suggested making the necessary combination to reach the claims in question. If not, then the combination which seems so logical seems so only by virtue of a hindsight analysis. That is the case here.

As a matter of law, the tripartite-complex-forming limitation cannot be disregarded. Accordingly, we respectfully request reconsideration and withdrawal of this ground for rejection.

Concluding Remarks

In view of the foregoing, applicants request reconsideration and allowance of their claims. If there are any remaining issues that might be resolvable by phone, applicants' attorney encourages the Examiner to call him at the number provided below.

Respectfully submitted,

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Date Monday, August 18, 2003

I hereby certify that this paper is being deposited with the United States Postal Service via First Class Mail under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, PO Box 1450. Alexandria, VA 22313-1450

Signed Sue Wilson
Sue Wilson